Immunology and Vaccine-Preventable Diseases

Immunology is a complicated subject, and a detailed discussion of it is beyond the scope of this text. However, an understanding of the basic function of the immune system is useful in order to understand both how vaccines work and the basis of recommendations for their use. The description that follows is simplified. Many excellent immunology textbooks are available to provide additional detail.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body ("self"), and to eliminate foreign ("nonself") material. This discriminatory ability provides protection from infectious disease, since most microbes are identified as foreign by the immune system. Immunity to a microbe is usually indicated by the presence of antibody to that organism. Immunity is generally specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity, active and passive.

Active immunity is protection that is produced by the person's own immune system. This type of immunity usually lasts for many years, often during a lifetime.

Passive immunity is protection by products produced by an animal or human and transferred to another human, usually by injection. Passive immunity often provides effective protection, but this protection wanes (disappears) with time, usually within a few weeks or months.

The immune system is a complex system of interacting cells whose primary purpose is to identify foreign ("nonself") substances referred to as antigens. Antigens can be either live (such as viruses and bacteria) or inactivated. The immune system develops a defense against the antigen. This defense is known as the immune response and usually involves the production of protein molecules by B lymphocytes, called antibodies (or immunoglobulins), and of specific cells, including T-lymphocytes (also known as cell-mediated immunity) whose purpose is to facilitate the elimination of foreign substances.

The most effective immune responses are generally produced in response to a live antigen. However, an antigen does not necessarily have to be alive, as occurs with infection with a virus or bacterium, to produce an immune response. Some proteins, such as hepatitis B surface antigen, are easily recognized by the immune system. Other material, such as polysaccharide (long chains of sugar molecules that make up the cell wall of certain bacteria) are less effective antigens, and the immune response may not provide as good protection.

Immunity

- Self vs. nonself
- Protection from infectious disease
- Usually indicated by the presence of antibody
- Generally specific to a single organism

Active Immunity

- Protection produced by the person's own immune system
- Often lifetime

Passive Immunity

- Protection transferred from another animal or human
- Effective protection that wanes with time

Antigen

- A live (e.g., viruses and bacteria) or inactivated substance capable of producing an immune response

Antibody

- Protein molecules (immunoglobulins) produced by B lymphocytes to help eliminate an antigen

Passive Immunity

- Transfer of antibody produced by one human or other animal to another
- Temporary protection
- Transplacental most important source in infancy

Sources of Passive Immunity

- Many types of blood or blood products
- Homologous pooled human antibody (immune globulin)
- Homologous human hyperimmune globulin
- Heterologous hyperimmune serum (antitoxin)

Passive Immunity

Passive immunity is the transfer of antibody produced by one human or other animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies will degrade during a period of weeks to months, and the recipient will no longer be protected.

The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last 1–2 months of pregnancy. As a result, a full-term infant will have the same antibodies as its mother. These antibodies will protect the infant from certain diseases for up to a year. Protection is better against some diseases (e.g., measles, rubella, tetanus) than others (e.g., polio, pertussis).

Many types of blood products contain antibody. Some products (e.g., washed or reconstituted red blood cells) contain a relatively small amount of antibody, and some (e.g., intravenous immune globulin and plasma products) contain a large amount.

In addition to blood products used for transfusion (e.g., whole blood, red cells, and platelets) there are three major sources of antibody used in human medicine. These are homologous pooled human antibody, homologous human hyperimmune globulin, and heterologous hyperimmune serum.

Homologous pooled human antibody is also known as immune globulin. It is produced by combining (pooling) the IgG antibody fraction from thousands of adult donors in the United States. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for postexposure prophylaxis for hepatitis A and measles and treatment of certain congenital immunoglobulin deficiencies.

Homologous human hyperimmune globulins are antibody products that contain high titers of specific antibody. These products are made from the donated plasma of humans with high levels of the antibody of interest. However, since hyperimmune globulins are from humans, they also contain other antibodies in lesser quantities. Hyperimmune globulins are used for postexposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Heterologous hyperimmune serum is also known as antitoxin. This product is produced in animals, usually horses (equine), and contains antibodies against only one antigen. In the United States, antitoxin is available for treatment of botulism and diphtheria. A problem with this product is serum sickness, an immune reaction to the horse protein.

Immune globulin from human sources is polyclonal; it contains many different kinds of antibodies. In the 1970s, techniques were developed to isolate and "immortalize" (cause to grow indefinitely) single B cells, which led to the development of monoclonal antibody products. Monoclonal antibody is produced from a single clone of B cells, so these products contain antibody to only one antigen or closely related group of antigens. Monoclonal antibody products have many applications, including the diagnosis of certain types of cancer (colorectal, prostate, ovarian, breast), treatment of cancer (B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma), prevention of transplant rejection, and treatment of autoimmune diseases (Crohn's disease, rheumatoid arthritis) and infectious diseases.

A monoclonal antibody product is available for the prevention of respiratory syncytial virus (RSV) infection. It is called palivizumab (Synagis). Palivizumab is a humanized monoclonal antibody specific for RSV. While certain antibody products like immune globulins interfere with live-virus vaccines, monoclonal antibody products specific to one, non-vaccine microbe do not interfere with live vaccines. Since palivizumab does not contain any other antibody except RSV antibody, it will not interfere with the response to a live virus vaccine.

Active Immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Unlike passive immunity, which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to survive infection with the disease-causing form of the organism. While exceptions (like malaria) exist, in general, once persons recover from infectious diseases, they will have lifelong immunity to that disease. The persistence of protection for many years after the infection is known as immunologic memory. Following exposure of the immune system to an antigen, certain cells (memory B cells) continue to circulate in the blood (and also reside in the bone marrow) for many years. Upon reexposure to the antigen, these memory cells begin to replicate and produce antibody very rapidly to reestablish protection.

Another way to produce active immunity is by vaccination. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the disease and its potential complications. Many vaccines also produce immunologic memory similar to that acquired by having the natural disease.

Monoclonal Antibody

- Derived from a single type, or clone, of antibody-producing cells (B cells)
- Antibody is specific to a single antigen or closely related group of antigens
- Used for diagnosis and therapy of certain cancers and autoimmune and infectious diseases, as well as prevention of transplant rejection

Antibody for Prevention of RSV

- Palivizumab (Synagis)
  - monoclonal
  - contains only RSV antibody
  - will not interfere with the response to a live-virus vaccine

Active Immunity

- Immune system produces antigen-specific humoral and cellular immunity
- Lasts for many years, often lifetime
- Sources
  - infection with disease-causing form of organism
  - vaccination

Vaccination

- Active immunity produced by vaccine
- Immunity and immunologic memory similar to natural infection but without risk of disease

Classification of Vaccines

- Live attenuated
  - viral
  - bacterial
- Inactivated

Inactivated Vaccines

- Whole
  - viruses
  - bacteria
- Fractional
  - protein-based
    - toxoid
    - subunit
  - polysaccharide-based
    - pure
    - conjugate

Live Attenuated Vaccines

- Attenuated (weakened) form of the "wild" virus or bacterium
- Must replicate to produce an immune response
- Immune response virtually identical to natural infection
- Usually produce immunity with one dose*
- Severe reactions possible
- Interference from circulating antibody
- Fragile – must be stored and handled carefully
- Viral: measles, mumps, rubella, vaccinia, varicella, zoster, yellow fever, rotavirus, intranasal influenza, oral polio**
- Bacterial: BCG**, oral typhoid

*except those administered orally
**not available in the United States

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of an adjuvant (e.g., aluminum-containing material added to improve the immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

Classification of Vaccines

There are two basic types of vaccines: live attenuated and inactivated. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.

Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacterium in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. The majority of live attenuated vaccines available in the United States contain live viruses. However, two live attenuated bacterial vaccines are available in the United States (Ty21a and BCG). BCG is not used as a vaccine, but as a treatment for bladder cancer.

Inactivated vaccines can be composed of either whole viruses or bacteria, or fractions of either. Fractional vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include toxoids (inactivated bacterial toxin) and subunit or subvirion products. Most polysaccharide-based vaccines are composed of pure cell wall polysaccharide from bacteria. Conjugate polysaccharide vaccines contain polysaccharide that is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine.

General Rule: The more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine

Live Attenuated Vaccines

Live vaccines are derived from "wild," or disease-causing, viruses or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. For example, the measles virus used as a vaccine today was isolated from a child with measles disease in 1954. Almost 10 years of serial passage using tissue culture media was required to transform the wild virus into attenuated vaccine virus.

To produce an immune response, live attenuated vaccines must replicate (grow) in the vaccinated person. A relatively small dose of virus or bacteria is administered, which replicates in the body and creates enough of the organism to stimulate an immune response. Anything that either damages the live organism in the vial (e.g., heat, light) or interferes with replication of the organism in the body (circulating antibody) can cause the vaccine to be ineffective.

Although live attenuated vaccines replicate, they usually do not cause disease such as may occur with the "wild" form of the organism. When a live attenuated vaccine does cause "disease," it is usually much milder than the natural disease and is referred to as an adverse reaction.

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection. The immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild virus. Live attenuated vaccines produce immunity in most recipients with one dose, except those administered orally. However, a small percentage of recipients do not respond to the first dose of an injected live vaccine (such as MMR or varicella) and a second dose is recommended to provide a very high level of immunity in the population.

Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (e.g., from leukemia, treatment with certain drugs, or human immunodeficiency virus [HIV] infection).

A live attenuated vaccine virus could theoretically revert to its original pathogenic (disease-causing) form. This is known to happen only with live (oral) polio vaccine.

Active immunity from a live attenuated vaccine may not develop because of interference from circulating antibody to the vaccine virus. Antibody from any source (e.g., transplacental, transfusion) can interfere with replication of the vaccine organism and lead to poor response or no response to the vaccine (also known as vaccine failure). Live attenuated vaccines are fragile and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated viral vaccines are measles, mumps, rubella, vaccinia, varicella, zoster (which contains the same virus as varicella vaccine but in much higher amount), yellow fever, rotavirus, and influenza (intranasal). Oral polio vaccine is a live viral vaccine but is no longer available in the United States. Live attenuated bacterial vaccines are bacille Calmette-Guérin (BCG—not currently available in the US) and oral typhoid vaccine.

Inactivated Vaccines

- Cannot replicate
- Less affected by circulating antibody than live vaccines
- Always require multiple doses
- Immune response mostly humoral
- Antibody titer diminish with time
- May require periodic supplemental booster doses
- Whole-cell vaccines
  - viral: polio, hepatitis A, rabies, influenza*
  - bacterial: pertussis*, typhoid*, cholera*, plague*
- Fractional vaccines
- Subunits: hepatitis B, influenza, acellular pertussis, human papillomavirus, anthrax
- Toxoids: diphtheria, tetanus

*not available in the United States

Inactivated Vaccines

Inactivated vaccines are produced by growing the bacterium or virus in culture media, then inactivating it with heat and/or chemicals (usually formalin). In the case of fractional vaccines, the organism is further treated to purify only those components to be included in the vaccine (e.g., the polysaccharide capsule of pneumococcus).

Inactivated vaccines are not alive and cannot replicate. The entire dose of antigen is administered in the injection. These vaccines cannot cause disease from infection, even in an immunodeficient person. Inactivated antigens are less affected by circulating antibody than are live agents, so they may be given when antibody is present in the blood (e.g., in infancy or following receipt of antibody-containing blood products).

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but "primes" the immune system. A protective immune response develops after the second or third dose. In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral. Little or no cellular immunity results. Antibody titers against inactivated antigens diminish with time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

Currently available whole-cell inactivated vaccines are limited to inactivated whole viral vaccines (polio, hepatitis A, and rabies). Inactivated whole virus influenza vaccine and whole inactivated bacterial vaccines (pertussis, typhoid, cholera, and plague) are no longer available in the United States. Fractional vaccines include subunits (hepatitis B, influenza, acellular pertussis, human papillomavirus, anthrax) and toxoids (diphtheria, tetanus). A subunit vaccine for Lyme disease is no longer available in the United States.

Polysaccharide Vaccines

Polysaccharide vaccines are a unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria. Pure polysaccharide vaccines are available for three diseases: pneumococcal disease, meningococcal disease, and *Salmonella* Typhi. A pure polysaccharide vaccine for *Haemophilus influenzae* type b (Hib) is no longer available in the United States.

The immune response to a pure polysaccharide vaccine is typically T-cell independent, which means that these vaccines are able to stimulate B cells without the assistance of T-helper cells. T-cell–independent antigens, including poly-

saccharide vaccines, are not consistently immunogenic in children younger than 2 years of age. Young children do not respond consistently to polysaccharide antigens, probably because of immaturity of the immune system.

Repeated doses of most inactivated protein vaccines cause the antibody titer to go progressively higher, or "boost." This does not occur with polysaccharide antigens; repeat doses of polysaccharide vaccines usually do not cause a booster response. Antibody induced with polysaccharide vaccines has less functional activity than that induced by protein antigens. This is because the predominant antibody produced in response to most polysaccharide vaccines is IgM, and little IgG is produced.

In the late 1980s, it was discovered that the problems noted above could be overcome through a process called conjugation, in which the polysaccharide is chemically combined with a protein molecule. Conjugation changes the immune response from T-cell independent to T-cell dependent, leading to increased immunogenicity in infants and antibody booster response to multiple doses of vaccine.

The first conjugated polysaccharide vaccine was for Hib. A conjugate vaccine for pneumococcal disease was licensed in 2000. A meningococcal conjugate vaccine was licensed in 2005.

Recombinant Vaccines

Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as recombinant vaccines. Five genetically engineered vaccines are currently available in the United States. Hepatitis B, human papillomavirus (HPV), and influenza (one brand) vaccines are produced by insertion of a segment of the respective viral gene into the gene of a yeast cell or virus. The modified yeast cell or virus produces pure hepatitis B surface antigen, HPV capsid protein, or influenza hemagglutinin when it grows. Live typhoid vaccine (Ty21a) is *Salmonella* Typhi bacteria that have been genetically modified to not cause illness. Live attenuated influenza vaccine has been engineered to replicate effectively in the mucosa of the nasopharynx but not in the lungs.

Polysaccharide Vaccines

Pure polysaccharide

- pneumococcal
- meningococcal
- *Salmonella* Typhi (Vi)

Conjugate polysaccharide

- *Haemophilus influenzae* type b (Hib)
- pneumococcal
- meningococcal

Pure Polysaccharide Vaccines

- Not consistently immunogenic in children younger than 2 years of age
- No booster response
- Antibody with less functional activity
- Immunogenicity improved by conjugation

Recombinant Vaccines

- Genetic engineering technology
- Viral: hepatitis B, human papillomavirus, influenza (one brand), live attenuated influenza
- Bacterial: *Salmonella* Typhi (Ty21a)

Selected References

Siegrist C-A. Vaccine immunology. In Plotkin SA, Orenstein WA, Offit PA. *Vaccines*, 5th ed. China: Saunders, 2008:17–36.

Plotkin S. Vaccines, vaccination, and vaccinology. *J. Infect Dis* 2003; 187:1347–59.

Plotkin S. Correlates of vaccine-induced immunity. *Clin Infect Dis* 2008; 47:401–9.

Principles of Vaccination

1